Brainstem Tumors: New era or more of the same?

George I. Jallo, MD
Nir Shimony, MD

Institute for Brain Protection Sciences
Johns Hopkins All Children’s Hospital
St. Petersburg, Florida

February 2, 2018
Distribution in Children and Adolescents (Age 0-19 Years) of Primary Brain and CNS Tumors by site

Neuro-Oncology

Epidemiology

- When looking at the entire population brainstem tumors account for 1.6% of all tumors and 3.8% of all malignant tumors (CBTRUS 2010-2014)
- Represents 10% of all brain tumors in the pediatric population
- 15-20% of posterior fossa tumors
- 80% Pontine location (In kids ~75% from brain stem tumors relate to the old entity DIPG)
- 150-200 new cases/year in North America
- Midbrain and medulla account for minority
- Occur in the first decade (more in the second half of it)
- Second peak in the 4th decade
- Slight male predilection

% of all CNS tumors

- astrocytoma
- astrocytoma 3-4
- ependymoma
- germ cell
- choroid plexus
- PNET
- brainstem glioma
- craniopharyngioma
- meningioma
- other
Few words on Anatomy

- Brainstem comprises the **midbrain, pons and medulla**
- Smallest part of the encephalon
- 6 cm by 3.5 cm wide
- 1/5 volume of the entire brain
- Highly complex neural circuitry (anatomically and functionally)
TELENCEPHALON (CEREBRUM)
- Conscious thought processes, intellectual functions
- Memory storage and processing
- Conscious and subconscious regulation of skeletal muscle contractions

METENCEPHALON (CEREBELLUM)
- Coordinates complex somatic motor patterns
- Adjusts output of other somatic motor centers in brain and spinal cord

DIENCEPHALON
THALAMUS
- Relay and processing centers for sensory information

HYPOTHALAMUS
- Centers controlling emotions, autonomic functions, and hormone production

MESENCEPHALON (MIDBRAIN)
- Processing of visual and auditory data
- Generation of reflexive somatic motor responses
- Maintenance of consciousness

METENCEPHALON (PONS)
- Relays sensory information to cerebellum and thalamus
- Subconscious somatic and visceral motor centers

MEDULLA OBLONGATA (MYELENCEPHALON)
- Relays sensory information to thalamus
- Autonomic centers for regulation of visceral functions such as cardiovascular, respiratory, and digestive activities
Very complex neurovascular anatomy
History of brainstem surgery

- Bailey 1930
  “Until some effective treatment other than surgery is devised gliomas of the brainstem will be hopeless problems for treatment”

- Matson, 1969
  “the location of these tumors in itself obviates the possibility of surgical removal”
  “regardless of specific histology they must all be classified as malignant tumors, since their location in itself renders them inoperable”


No distinction between different parts of the brainstem
History of brainstem surgery

• Mean survival in these early studies
  – 4 to 15 months
  – *Matson* then “should any patient with a clinical diagnosis of brainstem glioma still be alive as long as 18 months after diagnosis, with or without x-ray treatment, reinvestigation and probably surgical exploration is indicated as some other lesion is probably present”
History of brainstem surgery

- First introduced by Alvisi in 1962, then Pool in 1968.
- It was not until the advent of CT scans (1978) and MRI (1985) that these lesions were refined.
  - Hoffman et al, 1980
  - Epstein et al, 1986
Brainstem Tumors
Classification and Surgical Options

Not all brainstem tumors are alike.....
# Classification System for Brainstem Tumors

<table>
<thead>
<tr>
<th>Authors</th>
<th>Classification Scheme</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epstein, 1985</td>
<td>Intrinsic&lt;br&gt;Exophytic&lt;br&gt;Disseminated</td>
</tr>
<tr>
<td>Epstein, 1986</td>
<td>Diffuse&lt;br&gt;Focal&lt;br&gt;Cervicomedullary</td>
</tr>
<tr>
<td>Fischbein, 1996</td>
<td>Midbrain (diffuse, focal, tectal)&lt;br&gt;Pons (diffuse, focal)&lt;br&gt;Medulla</td>
</tr>
<tr>
<td>Albright, 1996</td>
<td>Focal (midbrain, pons, medulla)&lt;br&gt;Diffuse</td>
</tr>
<tr>
<td>Choux, 1999</td>
<td>Type 1: intrinsic tumor, diffuse&lt;br&gt;Type 2: intrinsic tumor, focal&lt;br&gt;Type 3: exophytic tumor, dorsal or lateral&lt;br&gt;Type 4: cervicomedullary tumor</td>
</tr>
</tbody>
</table>
Classification System

- Classification system based on MRI (Barkovich, 1991)
  - Location
    - Midbrain, pons, medulla
  - Focality
    - Diffuse or focal
  - Direction and extent of growth
  - Degree of brainstem enlargement
  - Evidence of hydrocephalus
  - Hemorrhage or necrosis
Clinical Presentation - Characteristic Signs & Symptoms

- Malignant tumor
  - Diffuse midline glioma, K27M mutant
    - Includes the old term – “DIPG”, which is the prototypical tumor describing brainstem tumors
  - High grade gliomas
- High Grade Gliomas (non K27M mutant)
- Embryonal tumors, C19MC-altered or not (PNETS is old term not for use)
- Lymphoma
- Metastases

- Benign or focal tumors
  - Location
  - Hydrocephalus
When classifications meet

- Barkovich and others designed the anatomic and radiographic classification of brainstem tumors
- WHO classification gave histology classification
- Brainstem tumors tend to be low grade tumors (that are located in a bad location), WHO II

So for years, the best solution was the exophytic tumor, low grade astrocytoma, which was easy to reach ...
In 2016, WHO published a supplement that lead to integrating molecular and genetics into the known histological classification from 2007.

For brainstem tumors the main change is with the deletion of DIPG, and the use of new group called “Diffuse midline glioma, H3 K27M–mutant”
What are “Diffuse midline glioma, K27M mutant”?

- Histone H3 K27M mutations are found in 80% of the tumors used to called DIPG (diffuse pontine gliomas)
- They are also found in other midline HGGs arising in the thalamus, cerebellum or spinal cord.
- About 75% of histone H3 mutations occur in \( H3F3A \), encoding the H3.3 isoform, and 20 – 25% of mutations occur in \( HIST1H3B \) or rarely \( HIST1H3A/C \), encoding H3.1
- \( ACVR1 \) mutations almost always occur concurrently with a \( HIST1H3B \) K27M mutation in diffuse pontine gliomas that present at less than 5 years of age. While H3.1 K27M mutations are also found in thalamic HGGs, \( ACVR1 \) mutations have only been identified in diffuse pontine gliomas. Hence, molecular subtyping can reveal today the origin of the tumor
- For patients harboring the K27M mutation the prognosis is less favorable
**Clinical signs and parameters**

**Diffuse tumors:**
- Duration of symptoms is short
  - Less than 3 months
- Deficits
  - Cranial nerve deficit 71-85%
    - Cranial nerves V, VI, VII, IX, X
  - Cerebellar ataxia 24-87%
  - Pyramidal tracts 43-80%
    - Motor, hyperreflexia, or sensory
- Obstructive hydrocephalus
  - More common for the focal benign tumors
  - 20-55%

**Focal tumors:**
- Raised Intracranial Pressure
  - Headaches, vomiting, lethargy
- Focal deficits
  - Cranial Nerve
    - Upper (CN III-VII)
    - Lower (CN IX-XII)
  - Pyramidal Tracts
  - Syndromes
- Duration of symptoms
  - Long prodrome
  - Failure to thrive
  - Extensive medical evaluation
MRI is the imaging modality and gold standard

- Multiplanar technique, with the sagittal plane the preferred image
- MRI devoid of artifacts
- High resolution
- New Sequences
  - DTI, MRS

**Malignant Tumors**
- Diffuse Midline Glioma
  - T1: isointense or slightly hypointense
  - T2: hyperintense
  - Gadolinium: Late in course or post treatment
- Medulla and Midbrain account for relatively few malignant tumors
**Pediatric brainstem gliomas**

**Diffuse intrinsic pontine gliomas (DIPGs) ~ 80%**
- **Course**
  - Typically rapid onset of symptoms (<3 months)
  - Rapid progressive clinical course
- **Pathology/Molecular characteristics**
  - Increasing evidence for a role of epigenetic alterations (H3K27M mutations)
  - Somatic mutations of ACVR1
- **Available treatment options**
  - Resection typically not possible due to location
  - Radiotherapy remains mainstay of treatment despite limited efficacy
  - Chemotherapies so far ineffective despite multiple studies
- **Prognosis**
  - Median survival 8-12 months

**Focal brainstem gliomas ~ 20%**
- **Pathology:**
  - Most commonly represent low grade gliomas
  - So far no evidence that epigenetic regulations may play a role
- **Available treatment options:**
  - May be resectable
  - Radiation and chemotherapy remain mainstay of therapy
- **Prognosis**
  - Median survival > 5 years

**Adult brainstem gliomas**

**Diffuse intrinsic pontine gliomas (DIPGs) 40-50%**
- **Course**
  - Can be more insidious onset of symptoms (>3 months)
  - Course may be less aggressive (although highly aggressive tumors occur)
- **Pathology/Molecular characteristics**
  - Low and high-grade gliomas occur
  - Molecular characteristics insufficiently understood:
    - Possible role of epigenetic alterations (H3K27M mutations)
    - Molecular characteristics are possibly distinct from supratentorial gliomas in adults
- **Available treatment options**
  - Resection often not possible due to location
  - Radiotherapy commonly used but with limited efficacy
  - Efficacy of chemotherapies is unclear
- **Prognosis**
  - Median survival 4.7-7.3 years

**Focal brainstem gliomas 50-55%**
- **Pathology:**
  - Typically represent high-grade gliomas
  - Molecular characteristics similar to supratentorial gliomas in adults
- **Available treatment options:**
  - Typically unresectable due to location
  - Radiotherapy remains mainstay of treatment
  - Possible benefit of chemotherapy
- **Prognosis**
  - Median survival 11.2 to 25 months
Diffuse Infiltrative Midline Gliomas
Diffuse Midline Glioma
Diffuse Midline Glioma
Diffuse Midline Glioma (Medullary Extension)
Focal Benign Brainstem Tumors: Juvenile Pilocytic Astrocytoma
Focal Medullary Ganglioglioma
No new deficits
Management for Brainstem Tumors

- **Hydrocephalus** – Consider treating first!
  - Endoscopic Third Ventricleostomy
  - Shunt diversionary procedure

- **Diffuse Midline Tumors**
  - Need for biopsy? (currently advocate only if part of trial)
  - Can the tumor be resected (e.g., Thalamopeduncular tumors)
  - Adjuvant therapy

- **Focal Tumors**
  - Surgery
    - Biopsy
    - Radical Resection
      - Risks versus Benefits
  - Adjuvant Therapy
    - Radiotherapy
    - Chemotherapy
Diffuse Midline Gliomas

- Surgery has no role in the current management for this tumor, yet the need for biopsy is advocated by many
  - Histology: high grade vs. low grade
  - Molecular subtyping – H3 K27M mutation?
- Radiation Therapy

Diagnosis Value and Safety of Stereotactic Biopsy for Brainstem Tumors: A Systematic Review and Meta-analysis of 1480 Cases
Radiotherapy

- Conventional therapy
  - 54 Gy (2cm margin) in 30 fractions over 6 weeks
  - Once daily

- Hypofractionated Radiotherapy
  - 39 Gy in 13 fractions (will be considered in cases with limited life expectancy, e.g. large diffuse tumor)

- Hyperfractionated Radiotherapy
  - Twice daily to 66, 70.2 and 75.6 Gy

Toxicity
- Steroid dependence

No substantial improvement in tumor control or survival, there is no support that hyperfractionated RT benefit long term adverse effects
Radiotherapy

- Brachytherapy
  - Iodine-125 implants (Chuba et al, 1998)
  - 27 children permanent implants
    - 10 patients with brainstem tumors
      - 8 patients with pontine gliomas
      - No complications
      - Results: pending
Chemotherapy for Brainstem Gliomas

- Benefit of chemotherapy is very questionable since most tumors will harbor K27M mutation, which shows low MGMT hypermethylation, that leads to lack of efficacy for Temozolomide.

- High-dose myeloablative chemo-therapy with autologous stem-cell rescue (ASCR) has also been explored, but the role of this approach in the treatment of pediatric high-grade gliomas remains unproven. Although can benefit if GTR achieved.
Chemotherapy for Brainstem Gliomas

- Several protocols for chemotherapy
  - Single agents used include:
    - Cyclophosphamide, ifosfamide, PCNU, cisplatin, carboplatin, iproplatin, AZQ, thiotepa, VP-16, topetecan, temodar
  - Multiagent therapy:
    - 8-in-1, MOPP, Iphosphamide VP-16 Mesna, cisplatin Ara-C VP-16
  - High dose with autologous rescue:
    - Busulphan thiotepa, thiotepa VP-16 BCNU
Molecular and immunologic therapy

- Always look for the kinase inhibitor option
- These drugs were found to improve overall survival in patients with BRAFV600E-mutant cancers
- ~10% of pHGG harbor this mutation
Diffuse Midline Gliomas Survival

Histone H3F3A and HIST1H3B K27M mutations define two subgroups of diffuse intrinsic pontine gliomas with different prognoses and phenotypes

David Castel1,2 · Cathy Philippe1 · Raphaëlle Calmon3 · Ludivine Le Dret1 · Nathalie Truffaut1 · Nathalie Boldaert1 · Mélanie Pagès7 · Kathryn R. Taylor4 · Patrick Saudinier5 · Ludovic Lacroix5 · Alan Mackay5 · Chris Jones5 · Christian Sainte-Rose6 · Thomas Blauwblomme6 · Felipe Andriolo7 · Stephanie Puget8 · Jacques Grill1,2 · Pascale Varlet1 · Marie-Anne Debily1,8

Received: 24 June 2015 / Revised: 8 September 2015 / Accepted: 10 September 2015 / Published online: 23 September 2015
## Current Open Protocols

<table>
<thead>
<tr>
<th>Study of Suberylanilide Hydroxamic Acid (SAHA) With Temsirolimus in Children With Diffuse Intrinsic Pontine Glioma (DIPG)</th>
</tr>
</thead>
</table>
| **Condition:** Diffuse Intrinsic Pontine Glioma  
**Interventions:** Drug: Vorinostat; Radiation: Radiation Therapy; Drug: Temsirolimus |

<table>
<thead>
<tr>
<th>Prolonged Exposure to Doxorubicin in Patients With Glioblastoma Multiforme and Diffuse Intrinsic Pontine Glioma</th>
</tr>
</thead>
</table>
| **Condition:** Glioblastoma (GBM); DIPG  
**Interventions:** Drug: Doxorubicin |

<table>
<thead>
<tr>
<th>Intra-arterial Chemotherapy for the Treatment of Progressive Diffuse Intrinsic Pontine Gliomas (DIPG)</th>
</tr>
</thead>
</table>
| **Condition:** Diffuse Intrinsic Pontine Glioma (DIPG)  
**Interventions:** Drug: Melphalan hydrochloride |

<table>
<thead>
<tr>
<th>Trial of Panobinostat in Children With Diffuse Intrinsic Pontine Glioma</th>
</tr>
</thead>
</table>
| **Condition:** Glioma  
**Interventions:** Drug: LBH589 |

<table>
<thead>
<tr>
<th>Molecular Profiling for Individualized Treatment Plan for DIPG</th>
</tr>
</thead>
</table>
| **Condition:** Diffuse Intrinsic Pontine Glioma (DIPG)  
**Interventions:** Other; Specialized tumor board recommendation; Radiation: Standard radiation therapy |

<table>
<thead>
<tr>
<th>Molecular Analysis of Samples From Patients With Diffuse Intrinsic Pontine Glioma and Brainstem Glioma</th>
</tr>
</thead>
</table>
| **Condition:** Diffuse Intrinsic Pontine Glioma; Brainstem Glioma  
**Interventions:** |

<table>
<thead>
<tr>
<th>Study of the Combination of Crizotinib and Dasatinib in Pediatric Research Participants With Diffuse Pontine Glioma (DIPG) and High-Grade Glioma (HGG)</th>
</tr>
</thead>
</table>
| **Condition:** Diffuse Intrinsic Pontine Glioma; High-grade Glioma  
**Interventions:** Drug: Crizotinib; Drug: Dasatinib |

<table>
<thead>
<tr>
<th>Abemaciclib in Children With DIPG or Recurrent/Refractory Solid Tumors</th>
</tr>
</thead>
</table>
| **Condition:** Diffuse Intrinsic Pontine Glioma; Brain Tumor, Recurrent; Solid Tumor, Recurrent; Neuroblastoma, Recurrent, Refractory; Ewing Sarcoma, Recurrent, Refractory; Rhabdomyosarcoma, Recurrent, Refractory; Osteosarcoma, Recurrent, Refractory; Rhabdoid Tumor, Recurrent, Refractory  
**Interventions:** Drug: Abemaciclib |

<table>
<thead>
<tr>
<th>Biological Medicine for Diffuse Intrinsic Pontine Glioma (DIPG) Eradication</th>
</tr>
</thead>
</table>
| **Condition:** Diffuse Intrinsic Pontine Glioma  
**Interventions:** Drug: Erlotinib; Drug: Everolimus; Drug: Dasatinib |

<table>
<thead>
<tr>
<th>Anti PD-1 Antibody in Diffuse Intrinsic Pontine Glioma</th>
</tr>
</thead>
</table>
| **Condition:** DIPG  
**Interventions:** Biological: MDV3100 |

<table>
<thead>
<tr>
<th>A Phase I Study of Ribociclib, a CDK4/6 Inhibitor, Following Radiation Therapy</th>
</tr>
</thead>
</table>
| **Condition:** High Grade Glioma; Diffuse Intrinsic Pontine Glioma; Diffuse High Grade Glioma  
**Interventions:** Drug: Ribociclib |

<table>
<thead>
<tr>
<th>A Phase I Study of Mebendazole for the Treatment of Pediatric Gliomas</th>
</tr>
</thead>
</table>
| **Condition:** Glioma; Diffuse Intrinsic Pontine Glioma; Low-grade Glioma; Brainstem Glioma  
**Interventions:** Drug: Mebendazole; Drug: Vinorelbin; Drug: Carcaptopin; Drug: Temozolomide; Drug: Bevacizumab; Drug: Imotocan |

<table>
<thead>
<tr>
<th>Diffuse Intrinsic Pontine Glioma (DIPG) Reirradiation (RefP)</th>
</tr>
</thead>
</table>
| **Condition:** Brain Cancer  
**Interventions:** Radiation: Radiation Therapy |

<table>
<thead>
<tr>
<th>A Study of DXP-7138 in Pediatric Patients With Relapsed or Refractory High Grade Gliomas</th>
</tr>
</thead>
</table>
| **Condition:** Glioblastoma; Diffuse Intrinsic Pontine Glioma  
**Interventions:** Drug: DXP-7138 |

<table>
<thead>
<tr>
<th>Pembrolizumab in Treating Younger Patients With Recurrent, Progressive, or Refractory High-Grade Gliomas or Diffuse Intrinsic Pontine Gliomas</th>
</tr>
</thead>
</table>
| **Condition:** Diffuse Intrinsic Pontine Glioma; Malignant Glioma; Recurrent Childhood Brain Neoplasms  
**Interventions:** Procedure: Diffusion Tensor Imaging; Procedure: Diffusion Weighted Imaging; Procedure: Dynamic Contrast-Enhanced Magnetic Resonance Imaging; Procedure: Dynamic Susceptibility Contrast-Enhanced Magnetic Resonance Imaging; Other, Laboratory Biomarker Analysis; Procedure: Magnetic Resonance Spectroscopic Imaging; Biological: Pembrolizumab; Procedure: Percutaneous Magnetic Resonance Imaging |

<table>
<thead>
<tr>
<th>Convective Enhanced Delivery of 134-I-AH9 for Patients With Non-Progressive Diffuse Pontine Gliomas Previously Treated With External Beam Radiation Therapy</th>
</tr>
</thead>
</table>
| **Condition:** Brain Cancer; Brain Stem Gliomas  
**Interventions:** Radiation: Radiolabeled monoclonal antibody 134-I-AH9 |

<table>
<thead>
<tr>
<th>Phase I Study of Mebendazole Therapy for Recurrent/Progressive Pediatric Brain Tumors</th>
</tr>
</thead>
</table>
| **Condition:** Medulloblastoma; Astrocytoma; Grade III; Glioblastoma; Anaplastic Astrocytoma; Brain Stem Neoplasms, Malignant; Oligodendrogliomas; Malignant Gliomas  
**Interventions:** Drug: Mebendazole |

<table>
<thead>
<tr>
<th>Prospective Trial of Two Hypofractionated Radiotherapy Regimens versus Conventional Radiotherapy in Diffuse Brainstem Gliomas in Children</th>
</tr>
</thead>
</table>
| **Condition:** Pediatric Brain Stem Gliomas  
**Interventions:** Radiation: Hypofractionated Arm (1); Radiation: Hypofractionated Arm (2); Radiation: Conventional Arm (3) |
Future Directions for Malignant Tumors

- Chemotherapy
  - New Agents
  - Local Delivery

- Radiotherapy
  - Interstitial therapy
  - Radiosensitizers, protectors
Local delivery methods of therapeutic agents in the treatment of diffuse intrinsic brainstem gliomas

C. Rory Goodwin, Risheng Xu, Rajiv Iyer, Eric W. Sankey, Ann Liu, Nancy Abu-Bonsrah, Rachel Sarabia-Estrada, James L. Frazier, Daniel M. Sciubba, George I. Jallo*

The Johns Hopkins University School of Medicine, Department of Neurosurgery, Baltimore, MD, USA

ARTICLE INFO

Article history:
Received 10 December 2015
Accepted 5 January 2016
Available online xxx

Keywords:
Brainstem glioma
Convection-enhanced delivery
Chemotherapy
Tumor
Interstitial continuous infusion
Intranasal delivery

ABSTRACT

Brainstem gliomas comprise 10–20% of all pediatric central nervous system (CNS) tumors and diffuse intrinsic pontine gliomas (DIPGs) account for the majority of these lesions. DIPG is a rapidly progressive disease with almost universally fatal outcomes and a median survival less than 12 months. Current standard-of-care treatment for DIPG includes radiation therapy, but its long-term survival effects are still under debate. Clinical trials investigating the efficacy of systemic administration of various therapeutic agents have been associated with disappointing outcomes. Recent efforts have focused on improvements in chemotherapeutic agents employed and in methods of localized and targeted drug delivery. This review provides an update on current preclinical and clinical studies investigating treatment options for brainstem gliomas.

© 2016 Published by Elsevier B.V.
Future Therapies for Diffuse Midline Brainstem Tumors

Convection-Enhanced Delivery for Diffuse Intrinsic Pontine Glioma Treatment

Zhiping Zhou, 1, * Ranjodh Singh, 2 and Mark M. Souweidane 1, 3, 4
Safety and efficacy of convection-enhanced delivery of gemcitabine or carboplatin in a malignant glioma model in rats

JEFFREY W. DEGEN, M.D., STUART WALBRIDGE, B.S., ALEXANDER O. VERTMEYER, M.D., EDWARD H. OLDFIELD, M.D., and RUSSELL R. LOSER, M.D.

Surgical Neurology Branch, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, Maryland; and Department of Neurosurgery, Georgetown University Medical Center, Washington, DC

Object. Convection-enhanced delivery (CED) can be used safely to perfuse regions of the central nervous system (CNS) with therapeutic agents in a manner that bypasses the blood–brain barrier (BBB). These features make CED a potentially ideal method for the distribution of potent chemotherapeutic agents with certain pharmacokinetic properties to tumors of the CNS. To determine the safety and efficacy of the CED of two chemotherapeutic agents (with properties ideal for this method of delivery) into the CNS, the authors perfused naïve rats and those harboring 9L gliomas with carboplatin or gemcitabine.

Methods: Dose-exclusion toxicity studies were performed by perfusing the striatum (10 μl, 24 rats) and brainstem (10 μl, 16 rats) of naïve rats with carboplatin (0.1, 1, and 10 mg/ml) or gemcitabine (0.4, 4, and 40 mg/ml) via CED. Efficacy trials involved the intracranial implantation of 9L tumor cells in 20 Fischer 344 rats. The tumor and surrounding regions were perfused with 40 μl of saline (control group, four rats), 1 mg/ml of carboplatin (four rats), or 4 mg/ml of gemcitabine (four rats) 7 days after implantation. Eight rats harboring the 9L glioma were treated with the systemic administration of 60 mg/kg of carboplatin (four rats) or 150 mg/kg of gemcitabine (four rats) 7 days postimplantation. Clinical, gross, and histological analyses were used to determine toxicity and efficacy.

Toxicity occurred in rats that had received only the highest dose of the CED of carboplatin or gemcitabine. Among rats with 9L gliomas, all control and systemically treated animals died within 26 days of tumor implantation. Long-term survival (120 days) and eradication of the tumor occurred in both CED-treated groups (75% of rats in the carboplatin group and 50% of rats in the gemcitabine group). Furthermore, animals harboring the 9L glioma and treated with intracranial CED of carboplatin or gemcitabine survived significantly longer than controls treated with intracranial saline (p < 0.01) or systemic chemotherapy (p < 0.01).

Conclusions: The perfusion of sensitive regions of the rat brain can be accomplished without toxicity by using therapeutic concentrations of carboplatin or gemcitabine. In addition, CED of carboplatin or gemcitabine to tumors in this glioma model is safe and has potent antitumor effects. These findings indicate that similar treatment paradigms may be useful in the treatment of glial neoplasms in humans.

KEY WORDS • glioma • carboplatin • chemotherapy • gemcitabine • convection-enhanced delivery • rat
Studies for Local Delivery

<table>
<thead>
<tr>
<th>Author</th>
<th>Delivery method</th>
<th>Subject</th>
<th>Compound</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carson et al. [43]</td>
<td>CED</td>
<td>Rat</td>
<td>Carboplatin</td>
</tr>
<tr>
<td>Sandberg et al. [41]</td>
<td>CED</td>
<td>Rat</td>
<td>Fluorescein isothiocyanate-dextran</td>
</tr>
<tr>
<td>Lonser et al. [61]</td>
<td>CED</td>
<td>Primate</td>
<td>Gd-bound albumin</td>
</tr>
<tr>
<td>Storm et al. [55]</td>
<td>CED</td>
<td>Primate</td>
<td>Carboplatin</td>
</tr>
<tr>
<td>Occhiogrosso et al. [42]</td>
<td>CED</td>
<td>Rat</td>
<td>Fluorescein isothiocyanate-dextran</td>
</tr>
<tr>
<td>Degen et al. [44]</td>
<td>CED</td>
<td>Rat</td>
<td>Carboplatin, Gemcitabine</td>
</tr>
<tr>
<td>Strege et al. [54]</td>
<td>CED</td>
<td>Primate</td>
<td>Carboplatin</td>
</tr>
<tr>
<td>Wu et al. [30]</td>
<td>CED</td>
<td>Rat</td>
<td>Carboplatin</td>
</tr>
<tr>
<td>Souweidane et al. [45]</td>
<td>CED</td>
<td>Rat</td>
<td>Carmustine, O6-benzylguanine</td>
</tr>
<tr>
<td>Souweidane et al. [64]</td>
<td>CED</td>
<td>Rat</td>
<td>IL13-PE38QQR</td>
</tr>
<tr>
<td>Lonser et al. [52]</td>
<td>CED</td>
<td>Human</td>
<td>IL13-PE38QQR, Glucocerebrosidase</td>
</tr>
<tr>
<td>Murad et al. [56]</td>
<td>CED</td>
<td>Primate</td>
<td>Gemcitabine</td>
</tr>
<tr>
<td>Hashizume et al. [60]</td>
<td>Intranasal</td>
<td>Rat</td>
<td>Telemorase inhibitor GRN163</td>
</tr>
<tr>
<td>Lee et al. [72]</td>
<td>Human neural &amp; mesenchymal stem cells</td>
<td>Rat</td>
<td>IFN-β, CD, 5-FC</td>
</tr>
<tr>
<td>Tange et al. [59]</td>
<td>ICI</td>
<td>Rat</td>
<td>Carboplatin, oxaliplatin</td>
</tr>
<tr>
<td>Thomale et al. [46]</td>
<td>CED</td>
<td>Rat</td>
<td>Carboplatin</td>
</tr>
<tr>
<td>Thomale et al. [52]</td>
<td>CED (multiple cannulas)</td>
<td>Rat</td>
<td>Carboplatin</td>
</tr>
<tr>
<td>Saito et al. [57]</td>
<td>CED</td>
<td>Human</td>
<td>Nimustine hydrochloride</td>
</tr>
<tr>
<td>Yoshimura et. [48]</td>
<td>CED</td>
<td>Rat</td>
<td>Temozolomide</td>
</tr>
<tr>
<td>Anderson et al. [58]</td>
<td>CED</td>
<td>Human</td>
<td>Topotecan</td>
</tr>
<tr>
<td>Luther et. al. [87]</td>
<td>CED</td>
<td>Rat and Primate</td>
<td>Theragnostic 131I-8H9</td>
</tr>
<tr>
<td>Sewing et. al. [49]</td>
<td>CED</td>
<td>Mouse</td>
<td>Carmustine</td>
</tr>
<tr>
<td>Zhou et. al. [50]</td>
<td>CED</td>
<td>Mouse</td>
<td>Small molecule kinase inhibitors: combinations of dasatinib, everolimus, perifosine</td>
</tr>
</tbody>
</table>
Clinical Significance for Local Delivery

Richard C. E. Anderson, M.D.,1 Benjamin Kennedy, M.D.,1 Candix L. Yanes, R.N.,1 James Garvin, M.D., Ph.D.,2 Michael Needle, M.D.,2 Peter Canoll, M.D., Ph.D.,3 Neil A. Feldstein, M.D.,1 and Jeffrey N. Bruce, M.D.1

Departments of 1Neurosurgery, 2Oncology, and 3Pathology and Cell Biology, Columbia University, College of Physicians and Surgeons, New York, New York
The Ultimate Focal Tumor
(Is the brainstem necessary??)

Yes, it is!!
Illustrative Case

- 8 yo boy otherwise healthy
- No past medical history
- Symptoms >12 months duration
- Headaches, Vision problems- double vision, Swallowing and coughing difficulty
Neurophysiological Monitoring

CN monitoring as well as corticospinal tracts

Anesthesiology team needs to be alert to any change in vital signs!!!
Displacement of the Cranial Nerve Nuclei

- Upper Pontine Tumor
- Lower Pontine Tumor
- Dorsal Exophytic Tumor
- Cervicomedullary Tumor
Stimulation intensity: 0.1mA

Cranial Nerve Mapping
Postoperative Visit: 2-4 weeks
MRI 3 months Postop
Management of Brainstem Tumors

Fig. 20.3 Treatment paradigm for brainstem gliomas.
Conclusions

• Malignant Brainstem Gliomas
  – New Classification (molecular)
  – Role for new treatment modalities
  – To biopsy or not biopsy

• Focal Benign Brainstem Tumors
  – Role of surgery
  – Adjuvant Therapies
    • Radiation- Mainstay Treatment
    • Chemotherapy – Which Agent?